REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-5 and 7-32 have been cancelled without prejudice or disclaimer for filing in one or more continuing applications. Claims 1-5 and 9-32 are directed to non-elected subject matter. SEQ ID NOs.: 6, 7, 9, and 10 are directed to non-elected species as set forth in the previous Office communication. Claim 6 is currently being amended. Claims 33-37 have been added. This amendment is fully supported by the originally-filed application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. After amending the claims as set forth above, claims 6 and 33-37 are now pending in this application.

The specification has been amended to delete embedded hyperlinks.

The undersigned is presently retrieving an electronic copy of Tables 1-4 so as to correct the spelling mistake identified by the Examiner. The entries in those tables should read "Fv" and not "Flv." However, at the time of filing this Amendment, the undersigned is not in possession of an easily accessible form of the Tables. Accordingly, Applicants will follow-up with a supplemental amendment correcting the tables within a short time.

II. Summary of the Office Action

Given the extensive nature of the Office Action, Applicants list below a brief summary of each of the Examiner's rejections.

(a) The Examiner deemed Applicants' election with traverse of Group 8 on the basis that the restriction between the amino acid of SEQ ID NO:8 and the nucleic acid encoding the protein phosphatase of SEQ ID NO:8 (Group III) to be unpersuasive. The restriction has been made final.

(b) The Examiner objected to portions of the disclosure that contained embedded hyperlinks and/or other form of browser-executable code.

(c) The Markush group of claims 6-8 is objected to as being in improper form because the proteins of SEQ ID NOs: 6-10 allegedly do not share a common utility nor a substantial structural feature that is essential to that utility.

(d) Claims 6-8 are rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well established utility

(e) Claims 6-8 are rejected under 35 U.S.C. § 112, first paragraph because allegedly one skilled in the art clearly would not know how to use the claimed invention.

(f) Claims 6-8 are rejected under 35 U.S.C. § 112, first paragraph because the claims allegedly encompass a "genus of naturally-occurring and man made phosphatases that are widely different in function" and, therefore, "many functionally unrelated polypeptides are encompassed within the scope of these claims."

(g) The recitation of "mammal" in claim 7 allegedly only describes "the functional features of the genus without providing any definition of the structural features of the species within the genus."

(h) Claim 8 is rejected because "allelic variations and splicing variants of human proteins are very common" and that, therefore, "the claimed genera are functionally diverse as they encompass polypeptides encoded by the same gene or different genes."

(i) Claims 6-8 are rejected under 35 U.S.C. § 112, first paragraph because, while the specification is enabling for a PP2C of SEQ ID NO: 8, it "does not reasonably provide enablement for a phosphatase of any type having an amino acid sequence that is 90% identical to SEQ ID NO: 8 or for a PP2C or any phosphatase having undisclosed homology to SEQ ID NO: 8."

(j) The specification does not support the broad scope of the claims because the specification "does not establish: (A) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful."

(j) Claims 6-8 are rejected under 35 U.S.C. § 112, second paragraph because the specification provides general discussion of certain phosphatase domains but "does not define them in relation to SEQ ID NO: 8."

(k) Claims 6-8 are rejected under 35 U.S.C. § 112, second paragraph because "it is unclear what is the difference among the recited domains and that, therefore, "without knowing which fragments of SEQ ID NO: 8 are encompassed, it is impossible to know the metes and bounds of the claim."

(l) Claims 6-8 are rejected under 35 U.S.C. § 103 as being unpatentable over Hillier et al., 1997, GenBank Accession AA292266, because Hillier et al., teach an mRNA that is similar to PP2C and that, therefore, it would have been obvious to use ["this EST"] to produce the encoded PP2C polypeptide.

III. Applicants' Response Overcomes Each of the Examiner's Rejections

(a) Applicants have cancelled claims 1-5 and 9-32

Without acquiescing to the Examiner's rationale for maintaining the restriction requirement, Applicants have cancelled withdrawn claims 1-5 and 9-32 directed to non-elected subject matter. Of course, Applicants reserve the right to file one or more continuing applications directed to the cancelled subject matter.

(b) Applicants have deleted embedded hyperlinks from the specification

In accordance with MPEP 608.01, Applicants have amended the specification to delete recitation of hyperlinks from various pages of the specification. Accordingly, Applicants respectfully request that the Examiner withdraw this objection.

(c) The Markush group of claim 6 is proper because the polypeptides of SEQ ID NOs: 8, 9, and 10 are all serine phosphatases

The Examiner deems the Markush group of claims 6-8 as being in improper form because the proteins of SEQ ID NOs: 6-10 allegedly do not share a common utility nor a substantial structural feature that is essential to that utility.

Applicants respectfully disagree and traverse this rejection. Applicants clearly characterize SEQ ID NOs: 8, 9, and 10, at pages 119-120 of the specification, as "serine threonine phosphatases." Applicants' characterization of SEQ ID NOs: 8-10 is based upon the amino acid sequences of the polypeptides, their level of homology with recognized phosphatase protein sequences, and their chromosomal location.

Nevertheless, Applicants have deleted all but the recitation to SEQ ID NO: 8 in claim 6. Accordingly, since there no longer exists a Markush group in presently amended claim 6, the Examiner's rejection is moot.

(d) The claimed invention has specific and substantial asserted utility

The Examiner rejected claims 6-8 under 35 U.S.C. § 101 as allegedly lacking support in the specification for either a specific and substantial asserted utility or a well established utility.

The Examiner recalls Applicants' classification of SEQ ID NO: 8 as a serine threonine phosphatase and as "PP2C" phosphatase via their comparison of SEQ ID NO: 8 to a mouse putative PP2C sequence, namely GenBank GI 12850332. However, the Examiner notes that "GenBank GI 12850332 was replaced by a newer version GI 26378394 that defines th [sic] polypeptide as unnamed protein product. The sequence search performed at the PTO did not

reveal any homology between SEQ ID NO: 8 and a protein for which PP2C activity was demonstrated." Office Action at page 5.

According to the Examiner, "it appears that the main utility of the polypeptide of SEQ ID NO: 8 is to carry out further research to identify the biological function and possible diseases associated with said function." Office Action at page 5. Applicants respectfully disagree with the Examiner's characterization of SEQ ID NO: 8 and that the "claimed invention has no specific or substantial asserted utility."

Applicants assert that the specification is replete with examples of the utility of the identified phosphatases. Applicants provide in the chart that follows below, exemplary support from the present specification as to the utility of a phosphatase of the present invention.

Applicants relate throughout the specification that the related phosphatases may be used to identify a compound that agonizes or antagonizes phosphatase activity. That compound may be then used therapeutically to modulate the activity of such a phosphatase in vivo. Thus, Applicants define that a "therapeutic effect" of the present invention "refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of the following: (a) an increase or decrease in the proliferation, growth, and/or differentiation of cells; (b) activation or inhibition (i. e., slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition ; and (e) enhancing the function of the affected population of cells. Compounds demonstrating efficacy against abnormal conditions can be identified as described herein." See lines 1-10 at page 40 of the specification.

Disclosed utility for a phosphatase with sequence of SEQ ID NO: 8	Citation
a "fragment" is "an amino acid sequence present in a phosphatase polypeptide. Preferably, such a sequence comprises at least 32, 45, 50, 60, 100, 200, or 300 contiguous amino acids of" SEQ ID NO: 8	page 16, lines 25-29 and page page 18, lines 19-25
"PP2C phosphatases are involved in many cellular processes, including" integrin signal transduction, the TAK1 signaling pathway, a cellular channel, a cyclin dependent kinase, and the Ras pathway	page 54, line 25 to page 55, line 8
for "detecting a polypeptide in a sample as a diagnostic tool for diseases or disorders"	page 55, lines 13-14
"can be used to produce antibodies or hybridomas"	page 56, lines 9-10
"can be used . . . such as for use in identifying pharmaceutical compositions"	page 56, lines 6-8
"can be used . . . for studying DNA/protein interaction"	page 56, lines 6-8
"to generate peptides capable of binding to a specific peptide sequence in order to generate rationally designed antipeptide peptides"	page 59, lines 12-13
for "detecting a phosphatase polypeptide in a sample"	page 59, lines 22-23
producing a "kit" for the purposes of "detection"	page 60, lines 21-27
"detecting a compound capable of binding to a phosphatase"	page 61, lines 7-10
"detecting an agonist or antagonist of phosphatase activity or phosphatase binding partner activity"	page 61, lines 12-20
"for treating a disease or abnormal condition by administering a substance that modulates the activity of a polypeptide" with sequence of SEQ ID NO: 8 "a functional derivative thereof, and a fragment thereof"	page 61, lines 24-28
for "modulating phosphatase associated activity in a mammal" by "administering to said mammal an agonist or antagonist to" SEQ ID NO: 8, "a functional derivative thereof, and a fragment thereof"	page 64, lines 6-10
for the production of "microarrays"	page 68, lines 1-15
for "detection of protein-protein interaction through phage display"	page 135-page 137
for identifying "compounds demonstrating the ability to modulate protein enzymes [preferably protein phosphatases] related to cellular signal transduction"	page 137, lines 18-24
for "identifying, evaluating or assaying the inhibition activity of protein enzymes, in particular protein phosphatases by the compounds"	page 138-page 143
for "recombinant production" of a serine/threonine phosphatase	pages 72-87
for developing "antisense" suppression of serine/threonine phosphatases	page 87-89
for producing "pharmaceutical formulations"	page 89-page 98

Applicants also have disclosed what kind of diseases and disorders can be treated according to the present invention and, moreover, how to correlate phosphatase activity with a particular disease condition. Thus, Applicants teach that the "relevance of a phosphatase gene to a particular diseased condition can be evaluated in order to effect treatment.

According to one embodiment of the present invention, microarray expression analysis is performed to establish expression profiles of various phosphatase genes according to the invention, and thereby identify the ones whose expression correlates with certain diseased conditions." See page 64, lines 16-20.

Applicants further relate at page 64, lines 21-29, that "such diagnostic measures may be used for a wide range of diseases, including cancer, pathophysiological hypoxia, cardiovascular disorders, Papillon-Lefevre syndrome, Cowden disease, ectordermal dysplasia, Moebius syndrome, Bjornstad syndrome, Bannayan Zonana syndrome, schizophrenia and hamartomas. Of particular importance is the diagnosis of various type of cancers. The diagnostic method of the present invention may be used to test for breast cancer, urogenital cancer, prostate cancer, head and neck cancer, lung cancer, synovial sarcomas, renal cell carcinoma, non-small cell lung cancer, hepatocellular carcinoma, pancreatic endocrine tumors, stomach cancer, gliobastoma, colorectal cancer, and thyroid cancer."

It has been well established that ". . . a disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a particular therapeutic application of the compound does contain an assertion of specific and substantial utility for the invention." *See*, MPEP 2107.02. As the Examiner is also aware, there is "no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility," MPEP 2107.02. "The applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re* Irons, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true."

However, the Examiner has made neither (i) a *prima facie* showing that the claimed invention lacks utility, nor (ii) provided a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. *In re* Gaubert, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975) ("Accordingly, the PTO must do more than merely question operability - it must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability."). The Examiner's allegations

that "the specification does not disclose a specific function of the polypeptides of SEQ ID NO: 8, its relationship to any disease, or any specific real world use," Office Action at page 5, clearly would not cause the skilled artisan to question Applicants' asserted utility for the phosphatase of SEQ ID NO: 8.

Indeed, Applicants provide in Exhibit A, a copy of an "NCBI Conserved Domain Search" analysis, which classifies the amino acid sequence of SEQ ID NO: 8 as a *bona fide* PP2C serine/threonine phosphatase, and shows the "significant alignment" of SEQ ID NO: 8 to other serine/threonine phosphatases.

Accordingly, Applicants state that the presently claimed invention does have specific and substantial asserted utility, which is credible to the person of ordinary skill in the art, a "real world use," and that the presently claimed invention is not limited to "carrying out further research." Therefore, Applicants assert that presently claimed invention has utility and respectfully request that the Examiner withdraw this rejection.

(e) The person skilled in the art would clearly know how to use the presently claimed invention

The Examiner rejected claims 6-8 under 35 U.S.C. § 112, first paragraph alleging that "one skilled in the art clearly would not know how to use the claimed invention." Office Action at page 6. Applicants disagree with the Examiner's assessment.

Applicants have detailed various methodological assays and diagnostic and therapeutic applications of the inventive phosphatase, as evidenced in the chart set forth above. See alsopages 55-71 and Examples 9, 10, and 11 at pages 133-145, where Applicants explicitly define steps and procedures so that the skilled person would know "how to use" the presently claimed invention. The person of ordinary skill in the art also would know how various aspects disclosed in the present specification could be implemented. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

(f) The specification correlates the structure and specific phosphatase function common to all members of the genus of PP2C serine/threonine phosphatases

Claims 6-8 are rejected under 35 U.S.C. § 112, first paragraph because the claims allegedly encompass a "genus of naturally-occurring and man made phosphatases that are widely different in function" and, therefore, "many functionally unrelated polypeptides are encompassed within the scope of these claims" like "alkaline" and "protein phosphatases." See page 7 of the Office Action. The Examiner continues that "the specification fails to provide the correlation between the structure and specific phosphatase function common to all members of the genus."

However, Applicants are not claiming any or all phosphatases. Claim 6 is directed to an isolated, enriched, or purified polypeptide that comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 8, *i.e.*, a PP2C serine/threonine phosphatase. Furthermore, the claim requires the polypeptide to be involved in at least one of integrin signal transduction, the TAK1 signaling pathway, a cellular channel, a cyclin dependent kinase, or the Ras pathway. See the paragraph bridging pages 54 and 55 for support for such activities.

Applicants have described in the application characteristic attributes of various phosphatase families, including that of the presently-claimed serine/threonine phosphatase depicted by SEQ ID NO: 8. See, for instance, page 2 of the specification, which discloses that protein tyrosine phosphatases, dual-specificity phosphatases, and serine/threonine phosphatases "share a 250-300 amino acid domain that comprises the common catalytic core structure." Applicants also characterize SEQ ID NO: 8 at pages 119-120.

Thus, there is, contrary to the Examiner's assertion, a limitation on the structure of the claimed phosphatase. Accordingly, Applicants are claiming what they regard as their invention, namely a PP2C-related, serine/threonine phosphatase polypeptide, that functions in a particular biological pathway.

(g) Claim 7 has been canceled

The Examiner states that the recitation of "mammal" in claim 7 allegedly only describes "the functional features of the genus without providing any definition of the structural features of the species within the genus." Without acquiescing to the Examiner's remarks, Applicants have canceled claim 7, simply for the purposes of expediting prosecution and, therefore, this rejection is moot. Of course, Applicants reserve the right to pursue the subject matter of the canceled claim in one or more continuing applications.

(h) Claim 8 has been canceled

Claim 8 is rejected because "allelic variations and splicing variants of human proteins are very common" and that, therefore, "the claimed genera are functionally diverse as they encompass polypeptides encoded by the same gene or different genes." Without acquiescing to the Examiner's remarks, Applicants have canceled claim 8, simply for the purposes of expediting prosecution and, therefore, this rejection is moot. Of course, Applicants reserve the right to pursue the subject matter of the canceled claim in one or more continuing applications.

(i)-(k) The presently claimed invention is enabled and supported by the written description

Claims 6-8 are rejected under 35 U.S.C. § 112, first paragraph because, while the specification is enabling for a PP2C of SEQ ID NO: 8, it "does not reasonably provide enablement for a phosphatase of any type having an amino acid sequence that is 90% identical to SEQ ID NO: 8 or for a PP2C or any phosphatase having undisclosed homology to SEQ ID NO: 8." According to the Examiner, the specification "does not establish" regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention or a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function.

Claims 6-8 also are rejected under 35 U.S.C. § 112, second paragraph because the specification provides general discussion of certain phosphatase domains but "does not define

them in relation to SEQ ID NO: 8." Claims 6-8 are rejected under 35 U.S.C. § 112, second paragraph because "it is unclear what is the difference among the recited domains and that, therefore, "without knowing which fragments of SEQ ID NO: 8 are encompassed, it is impossible to know the metes and bounds of the claim."

Firstly, the percent identity recited in independent claim 6 is literally supported by the present specification, for example at page 7, lines 1-8. Secondly, claim 6 does not require "effecting a specific requisite activity of a polypeptide" that comprises the amino acid sequence of SEQ ID NO: 8, nor does it require modification of SEQ ID NO: 8. Simply put, claim 6 is directed to the amino acid sequence of an isolated, enriched, or purified polypeptide. It is well known that conservative changes in amino acid occur naturally or can be made in order to arrive at a protein or polypeptide which retains the functionality of the original. Thus, the present invention encompasses naturally occurring, conservative changes in a polypeptide that render that polypeptide at least 90% identical to SEQ ID NO: 8. Alternatively, the amino acid sequence of SEQ ID NO: 8 could be "modified" so as to produce a polypeptide that has a sequence that is not more than 10% different to SEQ ID NO: 8.

With respect to the latter, the present specification discloses, in great detail, various domains of a serine/threonine phosphatase including the explanatory passages at pages 9-12, *i.e.*, definitions of "domain," "N-terminal domain," and "catalytic activity," that the skilled artisan would consider before creating such a modification. For instance, Applicants explain that "the N-terminal domain can be identified following a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the Nterminal boundary of the catalytic domain. Depending on its length, the N-terminal domain may or may not play a regulatory role in phosphatase function." See page 10, lines 3-8. Applicants also report in the specification that the term "catalytic domain"refers to "a region of the protein phosphatase that is typically 25-300 amino acids long and is responsible for carrying out the phosphate transfer reaction" and that the catalytic domain of protein phosphatases "is made up of 12 subdomains that contain highly conserved amino acid residues, and are responsible for proper polypeptide folding and for catalysis. The catalytic domain can be identified following a Smith Waterman alignment of the protein sequence against the non-

redundant protein database." See page 10, lines 8-17. At page 15, lines 3-11 of the specification, Applicants teach that "conserved regions [of a phosphatase of the present invention] differ by no more than 5 out of 20 nucleotides, even more preferably 2 out of 20 nucleotides or most preferably 1 out of 20 nucleotides."

Applicants also describe in detail how to analyze sequences to determine the existence of single nucleotide polymorphisms in a nucleic acid encoding a phosphatase, which could place the encoded phosphatase within the desired percent identity required by the claim.

Accordingly, it is well within the purview of the person of skill in the art to identify amino acid motifs within any of such domains and to determine whether one or more amino acids could be "modified" so as to arrive at a sequence that meets the limitations of the presently claimed invention. Further, the skilled artisan has at hand sophisticated sequence alignment programs, such as BLASTP and ProDom, which can readily identify conserved amino acids from an alignment of SEQ ID NO: 8 and other phosphatase proteins.

Thus, Applicants believe the claims are enabled and that the written description requirement more than sufficiently supports the rejected claims. Accordingly, Applicants respectfully request that the Examiner withdraw these rejections.

(l) The present claims are not rendered obvious by Hillier *et al.*

Claims 6-8 are rejected under 35 U.S.C. § 103 as being unpatentable over *Hillier et al.*, 1997, GenBank Accession AA292266, because Hillier *et al.*, allegedly teach an mRNA that is similar to PP2C and that, according to the Examiner, it would have been obvious "to use this EST to produce the encoded PP2C polypeptide." Office Action at page 12.

Applicants respectfully disagree and traverse this rejection. As the Examiner is aware, to establish a *prima facie* case of obviousness there must (1) some suggestion or motivation to modify the reference, (2) a reasonable expectation of success, and (3) the prior art reference must teach or suggest all the claim limitations. If the Examiner fails to establish a *prima facie* case, then Applicants are under no obligation to submit evidence of nonobviousness.

Firstly, Hillier *et al.*, depicts a nucleic acid cDNA clone, not an amino acid as presently recited in claim 6. Certainly, the presently claimed isolated, enriched, or purified polypeptide of SEQ ID NO: 8 does not read on such a DNA-based reference. Secondly, there is no motivation or suggestion anywhere in Hillier to modify the DNA sequence, *i.e.*, to identify the correct reading frame and produce a PP2C phosphatase family member, as the Examiner contends.

There exists nothing in Hillier to suggest to the person of ordinary skill in the art, at a time just prior to Applicants' invention, to transcribe and translate the described cDNA clone so as to produce a PP2C serine/threonine phosphatase protein that is involved in one or more of the recited biological pathways. There is nothing in Hillier to ensure that the "90%" sequence identity limitation recited in claim 6 is met.

Accordingly, there is nothing in Hillier, or in the conventional wisdom at the time the invention was made, to modify Hillier so as to arrive, successfully, at a polypeptide bearing all of the recited elements of claim 6; and, furthermore, the Examiner has not established a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date August 21, 2003

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NCBI

NCBI Conserved Domain Search

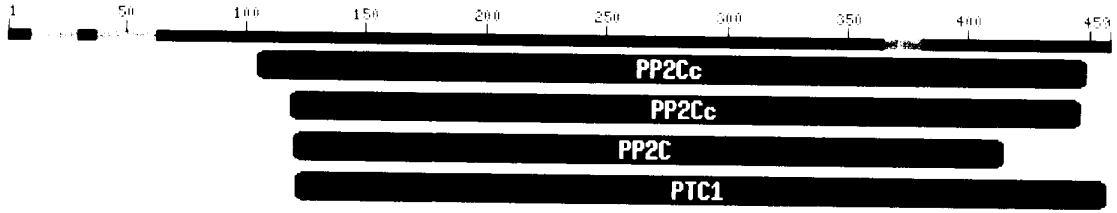
PubMed Nucleotide Protein Structure Taxonomy

RPS-BLAST 2.2.6 [Apr-09-2003]

Query= local sequence:
(459 letters)

Database: #cdd.v1.62
11,088 PSSMs; 2,717,223 total columns

Click on boxes for multiple alignments



Show Domain Relatives

- .. This CD alignment includes 3D structure. To display structure, download **Cn3D**!

PSSMs producing significant alignments:	Score (bits)	E value
gnl|CDD|16536 cd00143, PP2Cc, Serine/threonine phosphatases, family 2C, cata...	128	2e-30
gnl|CDD|14967 smart00332, PP2Cc, Serine/threonine phosphatases, family 2C, c...	117	4e-27
gnl|CDD|16734 pfam00481, PP2C, Protein phosphatase 2C. Protein phosphatase 2...	91.2	2e-19
gnl|CDD|10501 COG0631, PTC1, Serine/threonine protein phosphatase [Signal tr...	68.9	1e-12